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EXPERIENCES WITH ANTI - SYPHILITIC TREATMENT FROM THE PRE-SAL- VARSAN ERA TO THE PRESENT AND THEIR POSSIBLE BEARING ON PRESENT TREATMENT PRACTICE *

By L. W. HARRISON

SINCE I undertook the preparation of this paper I have realised that considerations of time and space would allow me to deal with the subject only superficially.

My first experience of the treatment of syphilis was thirty odd years ago in a hospital in India where the routine practice in early syphilis was to give the patient a mixture of liquor hydrarg. perchlor. and potassium iodide for only the six weeks or so that he was in hospital with open lesions.

Although my useful knowledge of syphilis at that time could have been written out on a sheet of notepaper, it did seem to me that a treatment of syphilis that lasted for only a few weeks must be hopelessly inefficient, and when the late Colonel F. J. Lambkin visited us to preach the advantages of a proposed new scheme of registration, under which syphilitic soldiers would be insured a minimum of two years' treatment by injections of mercury, I heartily supported him against the prevalent opposition. I suppose that at that time the treatment of syphilis in the Army must have been suffering from the change-over from the old regimental system to that under which the medical staff of the Army became welded into a corps. The old regimental system, whatever its drawbacks, and they were many, had the advantage that every man in a unit was known to the regimental doctor, who looked after him throughout his life in the Army in the way the family doctor looks after his patients' families. A good old regimental doctor told me once that he used to make his syphilitic patients take mercurial pills for a number of years. He said it was interesting

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to see how they began to look healthy again after about three years of this treatment.

My interest in the treatment of syphilis did not become really close, however, until 1909, when the accident of a medical officer's sudden illness caused my transfer as pathologist to the Military Hospital, Rochester Row, at that time under the command of Colonel Lambkin. Not very long ago it was unnecessary to explain the Military Hospital, Rochester Row, because everyone interested in syphilology knew it as the British military hospital devoted entirely to treatment of venereal diseases, investigation of new methods of treatment and instruction of Army medical officers in the subject. It had been a Guards' regimental hospital, and owed to Lambkin its assignment to V.D. about the year 1908, when the Royal Army Medical College and Queen Alexandra's Military Hospital, Millbank, were still in their infancy. Colonel Lambkin had pressed on the War Office the importance to the Army of medical officers being instructed in what were even then called modern methods of diagnosis and treatment of V.D., and it had been ordained that every medical officer of the R.A.M.C. should twice in his career, on joining and before the professional examination for promotion to major, receive some instruction at the Military Hospital, Rochester Row. You will remember that the year 1909 was after the discoveries of *S. pallida* and the Wassermann reaction, but before the publication of "606." About that time a great amount of interest was being taken in the use of certain pentavalent compounds of arsenic, especially atoxyl and arsacetin, and in atoxylate of mercury. Atoxyl had been reported by Thomas¹ in 1905 to be good for trypanosomiasis, and when Schaudinn suggested a relationship between *S. pallida* and trypanosomes it was not long before workers were trying its effect on syphilis, the first publication reporting good effects being that by Salmon² in 1907. By 1909 numerous workers had reported favourably on the effect of atoxyl in syphilis; Colonel Lambkin was particularly enthusiastic about it, and later I had an opportunity of verifying its good anti-syphilitic properties in the favourable blood reactions of over 200 cases of syphilis that had been treated at the Rochester Row Hospital solely with this drug. By the latter end of 1909, however, it had acquired

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a bad reputation owing to its tendency to cause blindness, and its use was rapidly being abandoned. At the time I joined the Rochester Row Hospital, Ehrlich's preparation arsacetin³ was in use, as it had been found by various workers to have just as great a trypanocidal and spirochætidal power as atoxyl, but its toxicity was only one-third or one-fourth.

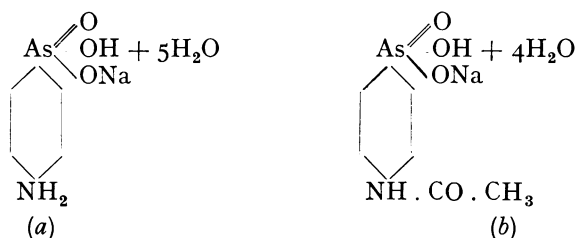


FIG. 1.—(a) Atoxyl. (b) Arsacetin.

At the same time atoxylate of mercury was also being given there and in many clinics on the strength of experimental work by Uhlenhuth and Manteufel,⁴ who had reported that it had acted better than atoxyl in trypanosomiasis, hen-spirillosis and experimental syphilis of rabbits. Lambkin was also trying to pluck up his courage to give the latest preparation from Ehrlich's laboratory, viz., "418," the disodium salt of Arsenophenyl-p-glycine⁵ ("Spirarsyl") which seems to have been the first of the trivalent arsenical remedies used in this field of medicine.

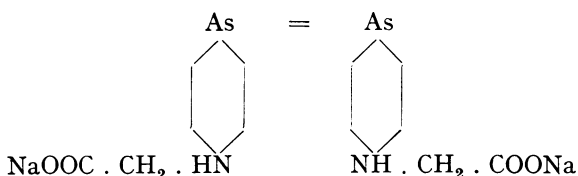


FIG. 2.—Sodium arsenophenylglycinate, "418," or "Spirarsyl," commonly termed Arsenophenylglycin.

We discussed the question of trying out a sample he had received from Ehrlich, but decided to await the receipt of more reports on its effects before doing so. It was just as well we did so, because the drug was in bulk, exposed to air and must by then have become decomposed. It was found by Alt,⁶ Neisser⁷ and others that, while its antisypylitic action was good, it was very easily oxidised and then gave rise to severe toxic effects.

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Neisser, in fact, later reported some deaths from it. Our sample of arsenophenylglycin would probably have had such toxic effects as would later have seriously deterred us from taking up its great successor "606," but it is only fair to mention that, in his article on it published six years later, Neisser,⁷ on the strength of five years' work with it, expressed the view that it deserved to be used more. He was particularly impressed by its causing no discomfort when injected intramuscularly, and he thought that it might be used when intravenous injections of salvarsan or neosalvarsan were impracticable.

Colonel Lambkin's departure from Rochester Row and the bad name which arsenic had by that time acquired amongst syphilologists resulted in our falling back in the winter of 1909-10 and the subsequent spring on treatment by mercurial injections. It gave me an opportunity of learning for myself the therapeutic properties of the insoluble preparations of mercury that were being given by the intramuscular route at that time. I learnt enough to make me regard the outlook for a syphilitic patient treated only by mercury with gloomy foreboding. It was quite usual for patients to relapse with clinical signs of syphilis during courses of intramuscular injections, and only three months after completion of the two years of regular treatment which was then prescribed in the Army as a matter of course for early syphilis no less than 42 per cent. gave positive reactions to the original Wassermann reaction, while over 75 per cent. were positive to Stern's modification of this test. It is interesting now to see the touching faith which many practitioners still have in treatment for two years with mercurial pills after what we know now to be quite an inadequate treatment by the modern arsenical remedies. To anticipate, during the period between 1909 and 1913 we⁸ investigated the incidence of clinical relapses in cases of primary and secondary syphilis by studying the syphilis case sheets of the Brigade of Guards returned to the War Office between 1906 and 1912, and in the 378 cases judged to have been well treated by mercurial injections or inunctions for at least a year. I found that in the first year 315 had relapsed clinically at least once (more than half of them two or more times). The results of the investigation are shown in Table I., in which are contrasted the effects of purely mercurial treatment

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carried out steadily for a year with those of a short course of salvarsan and mercury lasting no longer than three months.

TABLE I.—*Total Relapses and Average Time lost by each Soldier in Hospital and attending as an Out-Patient under Treatment with Mercury and with Mercury and Salvarsan respectively, during the first year.* (From Paper by Gibbard and Harrison, Int. Med. Congress, 1913.)

Treatment	Total cases	Average number of days in hospital on first admission	Clinical relapses				Percentage of clinical relapses	Average time lost by each man in days		
			Once only	Twice only	Three or more times	Total number which relapsed		In hospital	Attending as an out-patient	Total
Mercury alone .	378	42.0	151	115	49	315	83.0	66.2	17.6	83.8
Mercury and Salvarsan .	152	23.2	6	0	0	6	3.9	25.2	15.8	41.0

What I have said may help those of you who took up the treatment of syphilis after 1910 and take for granted the effects of modern treatment to understand the excitement of syphilologists in 1910 when they read the first report by Alt ⁹ of the effects of a drug known as "606,"

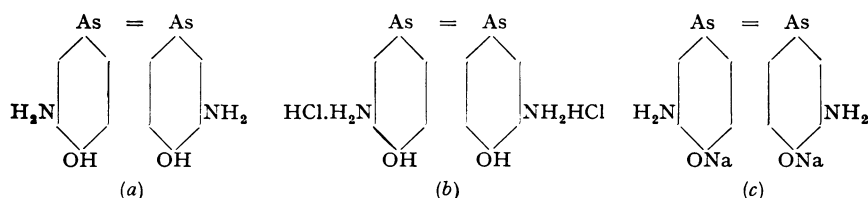


FIG. 3.—(a) 3:3' diamino-4:4'-dihydroxyarsenobenzene or "592," the insoluble arspenamine base. (b) The dihydrochloride of (a), or "606," or **arsphenamine**. (c) Disodium arspenamine, into which arspenamine must be converted for intravenous injection.

or the Ehrlich-Hata remedy. Alt's paper was read first at a meeting of the Medical Society of Magdeburg on March 3rd, 1910, and it is interesting to read in the proceedings ¹⁰ that, after Schreiber had demonstrated the effect of the remedy on a number of cases of syphilis, two members taking part in the discussion said in effect that the results were quite nice, but no better than they could obtain with mercury. We learnt that the remedy

could not be put on the market until it had been well tried out in reliable clinics. After we had represented to Professor Ehrlich that we were in a very favourable position to test it, he was good enough to send us a supply and continued to meet our requests for more until "606" was put on the market under the trade name "Salvarsan" towards the end of 1910, about eight months after the publication of Alt's paper. From our receipt of the first doses of "606" until August, 1914, we took full advantage of the fact that as long as a syphilitic soldier remained in the Army he could be observed, and we carried out a systematic investigation of the remedy. As soon as we learnt that it was not a one-dose cure of syphilis, we set out to discover what was the minimum amount of it which would suffice to cure an average case of early syphilis. In the first series of cases each received a single dose of "606" by the intramuscular or deep subcutaneous route. Less than fifty of these had been given when our attention was drawn to a paper by Schreiber and Hoppe¹¹ on intravenous injection of the remedy, and intramuscular and deep subcutaneous injections were gladly abandoned because of the agony they caused. Our next series received each a single dose of 0.6 gm. intravenously, and then without waiting for results successive series were treated as follows. (1) Two intravenous of 0.6 gm. at two weeks' interval. (2) One of 0.6 followed by three of 0.3 gm. at two-weekly intervals. (3) Three of 0.6 gm. at two-weekly intervals and four of calomel cream, gr. $\frac{3}{4}$ in each, at weekly intervals, total length of course, one month. (4) One of 0.6 gm. "606," then nine of mercurial cream, Hg gr. 1 in each, at weekly intervals, and at the end one of 0.6 gm. "606." (5) A similar course, but with an initial dose of 0.3 gm. "606," soon abandoned for reasons to be given later, and finally (6) a series in which each patient received one of 0.6 gm. "606," five of Hg at weekly intervals, one of 0.6 gm. "606," five more Hg and a final dose of 0.6 gm. "606." The results of these courses were watched either by ourselves, or in the case of patients moved to other stations by medical officers there, who reported the clinical condition to us and sent us specimens of blood whenever we called for them.

It may be convenient at this stage to comment on the results of the different courses of treatment during the

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pre-war period and the lessons derived therefrom either then or later.

The first concerns the deep subcutaneous or epifascial injections. Although this route proved quite an impracticable one for "606," the experience of it led me to two discoveries which seemed useful. The first related to the therapeutic value of the route and the second to the size of the individual dose.

With regard to route, in a certain number of the cases injected deep subcutaneously sloughs formed and on removal, sometimes many months after the injections, they were found by Colonel Beveridge at the R.A.M. College to contain comparatively large amounts of arsenic. Thus in one-third of a slough removed more than a year after an injection of 0.6 gm. "606" was found 0.04 gm. arsenious oxide,⁸ which would correspond to about a fifth of the original dose, while in another removed four months after an injection of 0.4 gm. Colonel Beveridge and Captain Dunbar Walker¹² found an amount of arsenic equivalent to 0.075 gm. of the remedy. Yet in spite of the comparatively indifferent absorption of the original dose which these analyses suggested, the immediate effects had been what we then commonly called magical in healing of clinical lesions, and without any other treatment the Wassermann reaction had in due course become negative in a high proportion of the cases, as is shown in Table II. extracted from a paper published by Colonel Gibbard¹³ and myself in 1911. I doubt if anyone to-day would expect such results from a single injection.

At the time we made this discovery we had not found the results much better after a single dose of 0.6 gm. salvarsan given intravenously than after a single one given deep subcutaneously. I was wondering why a single dose failed to cure when it had such marvelous effects on open lesions, and a possible explanation seemed to be that at the time of its administration a certain proportion of the spirochætes were inaccessible. If this was the case, then, seeing how well a deep subcutaneous injection acted in spite of its being absorbed very indifferently, it seemed possible that a single dose of 0.3 gm. "606" given intravenously would do as much good eventually as one of 0.6 gm., because it might well be that a large portion of a dose of 0.6 gm. given intra-

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TABLE II.—*Serum Reactions after a Single Deep Subcutaneous Injection of Salvarsan*

Interval between injection and blood test	Positive before injection	Wassermann reactions			
		After injection			
		Positive	Weaker	Negative	Positive after being negative
Weeks					
1 to 2	17	13	1	3	0
2 „ 3	15	8	3	4	0
3 „ 4	10	4	4	2	0
4 „ 5	15	4	1	8	2
5 „ 6	7	1	1	5	0
10 „ 14	24	0	2	21	1
14 „ 18	28	3	1	18	6
18 „ 26	7	0	0	4	3

venously was excreted before it could reach spirochaetes buried within cellular infiltrates; that before these spirochaetes could be destroyed they would have to be laid bare by absorption of infiltrates. I ought to explain here that I had found that *S. pallida* seemed to disappear from the secretion of early syphilitic lesions as rapidly after 0.3 gm. "606" intravenously as after 0.6 gm. subcutaneously. Accordingly, I suggested our treating a series of cases with an initial dose of 0.3 gm. "606," then nine intramuscular injections of mercury and lastly a dose of 0.3 gm. "606." This course was very quickly found to be useless. Patients relapsed clinically before the series of intramuscular injections of mercury had been completed. The inferences seemed to be (a) that, other things being equal, the therapeutic effect of a deep subcutaneous or intramuscular injection of "606" (or of probably any other arsenobenzene compound) must be greater than that of the same compound given intravenously, and (b) that the bigger the individual dose the more lasting its effect. I believe that subsequent experiences have proved both of these inferences to be correct.

During the war at various weekly meetings of medical officers in military hospitals which I commanded I said that, if a method of giving "606" or "914" deep

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subcutaneously or intramuscularly without undue pain could be discovered, it would oust the others, because the results would be so much better. I judged the subcutaneous route would act better because by fixing the remedy in the tissues it would give a better opportunity for the formation of that derivative which we know is necessary to the therapeutic action. This was taken up in two military hospitals, in each of which a series of patients received a course of deep subcutaneous injections of "914" (dissolved in an anæsthetic solution to

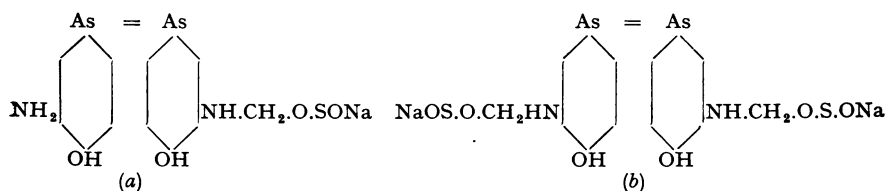


FIG. 4.—Alternative formulæ of "914" or neoarsphenamine. (a) The original formula sodium 3 : 3'-diamino-4 : 4'-dihydroxyarsenobenzene-N-methylenesulphoxylate. (b) The formula ascribed by A. D. Macallum to the French form of neoarsphenamine.

make it tolerable), and the results were compared with those of a course of "606" given intravenously to a series of patients in the same stages of the disease. The published report¹⁴ on the results related to 151 cases treated by the subcutaneous route and 251 by the intravenous. In the intravenous series each received a total of 2.8 gm. "606" in seven doses of 0.3 to 0.5 gm., given over a period of fifty days, and in the subcutaneous series the total amounts of "914" administered in forty-three days were 4.3 gm. to 27 patients, 4.05 gm. to 40 and 3.9 gm. to 99, so that the total amount of "914" averaged in terms of arsenic less than the total "606." The results in the two hospitals agreed very closely, and were combined as shown in Table III.

The table shows that in spite of the well-known fact that "914" given intravenously is less active therapeutically than is its equivalent in "606" given intravenously, yet when given subcutaneously it resulted in approximately 12 per cent. more negative reactions in primary and in secondary cases than did a little more than its arsenical equivalent in the form of "606" given intravenously.

The second point, as to the effects of the larger indivi-

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TABLE III.—*Comparison of Effect of a Course of Neo-salvarsan administered by the Deep Subcutaneous Route with that of an approximately equivalent amount of Salvarsan administered Intravenously.* (From paper by Harrison, White and Mills.¹⁴)

Stage	Route	Cases	Wassermann reactions at end of course							
			+		±		+ ₌		—	
			No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Primary .	{ S.C.	67	0	0	0	0	3	4.4	64	95.5
	{ I.V.	79	3	3.7	6	7.5	4	5.0	66	83.5
Secondary.	{ S.C.	76	11	14.4	4	5.2	7	9.2	54	71.0
	{ I.V.	141	35	24.8	16	11.3	8	5.6	82	58.1
Tertiary .	{ S.C.	18	10	55.5	3	16.6	1	5.5	4	22.2
	{ I.V.	31	18	58.0	1	3.2	3	9.6	9	29.0

Explanation.—S.C. = Subcutaneous (" 914 "); I.V. = Intravenous (" 606 "); + = positive; ± = doubtful; +₌ = almost negative; — = negative.

dual dose, is supported by our later experience. In our pre-war series the usual individual dose of " 606 " was 0.6 gm., and in the series of primary and secondary cases treated by two doses of " 606 " separated by nine injections of mercury, as well as in that treated with three doses of " 606 " with ten of mercury, the serum reactions at the end of the course were practically always negative. Such immediate results have not been achieved since, although the total amount per course was increased at the beginning of the war, and is now in terms of arsenic more than twice the total of any of our pre-war courses, and I am convinced it is partially because since 1914 we have used smaller individual doses. At the beginning of the war I had to devise a course which could be given safely in a much smaller time than ten weeks and would be followed by fewer relapses (within a year after suspension of treatment) than any pre-war course, our best results then having been represented by 28 per cent. clinical and

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serological relapses a year or more after the last injections. I aimed at first to increase the total from 1.8 gm. to 2.4 gm. "606" and to give it in a month, and judged that, unless the individual doses were reduced, there would be several deaths from hæmorrhagic encephalitis. Accordingly, the individual dose was reduced to 0.3 gm. "606" at first, and though it was increased later, it never reached its pre-war size. It might be argued that the difference between the immediate results of our pre-war courses and those being given to-day in this country is due to the lower therapeutic value of "914," which in this country has now supplanted "606." This may be so to some extent, but Table III. shows worse immediate results with 2.8 gm. original "606" given intravenously than we had got from 1.8 or even only 1.2 gm. in our pre-war courses.

There is further support for my contention that a small total dosage given in a few large individual doses will have a better therapeutic effect than a rather larger total dosage given in smaller individual doses in the report on the analysis of records collected in five countries under the auspices of the League of Nations Health Organisation.¹⁵ In this the Danish results were shown to be on the whole the best of those under "intermittent" treatment, and in oral discussion it was attributed partly to the fact that syphilologists in Denmark, under the influence of Professor Rasch's teaching, have tended to give quite high individual doses of "914." It was this which led the Experts' Committee to make a recommendation "To employ a comparatively heavy individual dosage of the arsenobenzene and of the bismuth or mercurial compounds."

In this matter I admit myself to be rather a convert. At one time I thought that, so long as one gave an individual dose which would cause the spirochætes to disappear from the secretion of early lesions, what mattered was the total dosage per course. My discovery that our small total but large individual dosage course employed before 1914 gave better immediate results than the larger total, but smaller individual dosage courses given during the war and later prepared me to agree with Rasch's views when these were backed by the Danish results in the League's inquiry. It is interesting to see how frightened syphilologists to-day seem to be of giving

large individual doses of neoarsphenamine, considering that when neosalvarsan was first published we regularly gave doses of 0.9 gm. even twice a week, and I often gave single doses of 1.2 gm., as I believe do some French syphilologists to-day. Schreiber,¹⁶ who was, I think, the first to publish a paper on the administration of neosalvarsan, at first recommended huge doses, such as 0.9, 1.2, 1.35 and 1.5 gm., to men on alternate days, and mentioned that he had given as much as 6.0 gm. within seven days. In this article he reported on 97 cases in which no serious toxic effect appears to have occurred, but later, in 1912, he reported some serious exanthemata and recommended some caution in the initial dosage, e.g., 0.4 to 0.6 gm. for men, with an interval of two weeks before the next dose, mercury being given meantime. As Schreiber mentioned in his second article, Iversen was also in the habit of giving from 4 to 6 gm. neosalvarsan in a week. Although one would hesitate to give such heroic doses as these, I would again suggest that we might get better results with a smaller total dosage and therefore with less dermatitis, etc., by giving larger single doses.

The subject of individual dosage leads naturally to individual type of preparation and to an experience just after the war which showed that certain arsphenamine preparations of apparently the same chemical composition can differ very strongly in therapeutic effect. Shortly after the war some of us, members of the Medical Research Council's Salvarsan Committee, noticed that clinical relapses were occurring rather frequently after the first course of treatment, and investigation by Dale, White and colleagues¹⁷ showed that certain brands of "914" which had been used in the treatment of these cases were inferior in trypanocidal and spirochæticidal effect to another with which they were compared at the same time. A conference with the manufacturers concerned revealed that all manufacturers were not using the same method, and that some were preparing a product which resembled a mixture of what we now call sulpharsphenamine with neoarsphenamine, rather than the latter compound alone. I learnt from this experience that it is a good thing to test one's arsphenamine preparations periodically to see that they retain their power of causing rapid disappearance of *S. pallida* from the secretion of early

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lesions, and also that the group of remedies now officially termed sulpharsphenamine is far inferior to neoarsphenamine when given intravenously. Animal experiments

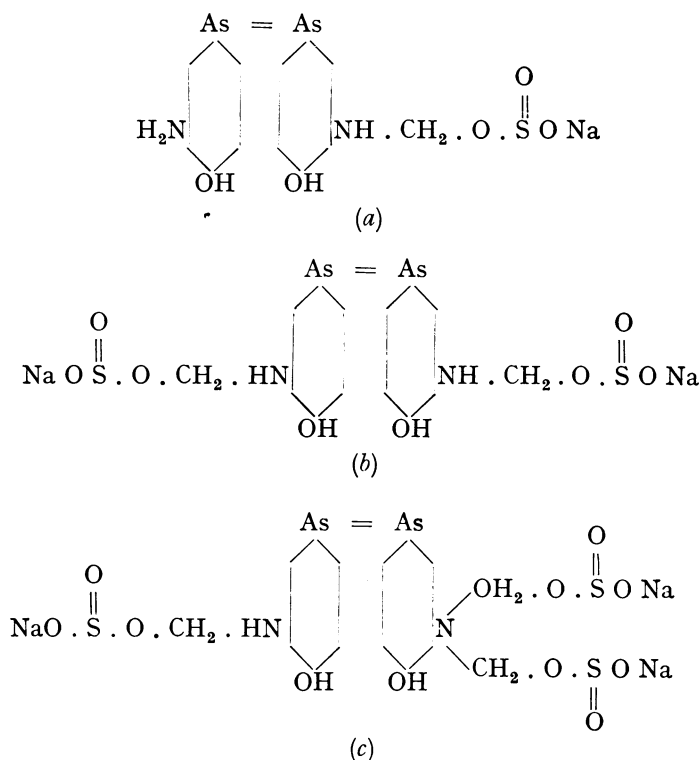


FIG. 5.—Alternative formula of **sulpharsphenamine**. (a) Sulfarsenol brand, of Lehnhoff-Wyld. (b) American formula, of Voegtlin, Johnson and Dyer. (c) Formula of one British brand (private communication).

seem to show that, when given deep subcutaneously, the effect of sulpharsphenamine is enhanced sufficiently to make it equal to neoarsphenamine given intravenously. Unfortunately the sulpharsphenamine preparations lose their advantage of being tolerable when given subcutaneously in their proneness to cause purpura.

Before leaving this subject it may be of interest to reflect a little on the chemical structure of these compounds, illustrated in Figs. 3, 4 and 5, in relation to the pain they cause when injected subcutaneously or intramuscularly and also to their therapeutic effects. The following remarks are made with great diffidence, as I am no chemist. With regard to pain, it is of course well

known that "606" is the worst, that "914," or neoarsphenamine, to give it its official name, hurts too much to make the subcutaneous route practicable for it in routine work, and that sulpharsphenamine is commonly given by this route. The difference between them, especially between neo- and sulpharsphenamine, is in the combination with the NH_2 group. With regard to the question of therapeutic effect, the amino combination again seems to be the important factor. In the case of "606," in the form it enters the circulation, the NH_2 group is combined only with the benzene ring. In the case of "914," one (or both) is, so to speak, tied up. In Fig. 4 two alternative graphic formulæ for "914" are shown, and respecting these Schlossberger¹⁸ states that the second, with both NH_2 groups substituted, is less toxic, but also less active therapeutically. He adds that the neoarsphenamine of commerce is a mixture of the mono- and the disubstitution products. In the case of sulpharsphenamine the extra atom of oxygen has made the product more stable, less toxic and less active therapeutically when given intravenously. Fig. 5 shows three alternative formulæ, the original one by Lehnhoff-Wyld, the American of Voegtlin, Johnson and Dyer, and that ascribed to his preparation by one of the British makers (private communication). One is tempted to speculate if the products sold in this country are closer to the French than to the American and if the difference accounts for the fact that, although our sulpharsphenamine certainly does seem to be more prone to cause purpura than does our "914," yet, judging by the literature, it is certainly not so bad in this respect as the American products of this type.

To revert to pre-war experience. I should like here to mention another systematic investigation of salvarsan which was carried out at the same time as ours by Marine-Oberstabsarzt Gennerich,¹⁹ because I believe that no finer results than his have ever been published. Gennerich took advantage of the control over his cases which his position as a naval surgeon gave him to carry out the most scrupulous observation of them for long after suspension of treatment. His paper giving his latest results, which was published in 1914 in celebration of Ehrlich's sixtieth birthday, ought to be read by everyone who is interested in discovering the perfect scheme of

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treatment of early syphilis ; when I first read it I was filled with envy because at the time our best results looked very poor in comparison with his. Ours showed approximately 28 per cent. of clinical and serological relapses in the primary and secondary cases treated with 1.2 to 1.8 gm. "606" in two to three doses and nine to ten mercurial injections and observed for twelve months or longer. His showed in the last series of cases, observed for a year or longer clinically, by blood tests and by examination of the spinal fluid after suspension of treatment, 92 primary cases with 3 relapses (1 serological and 2 with slight changes in the fluid), and 70 early secondary cases with 4 relapses (3 clinical and 1 serological). For 3 of these relapses he blamed the use of neosalvarsan which, after trial, he considered to be very inferior to salvarsan. His courses of treatment had been increased after 1910 until in the year ending March, 1914, they had become as follows. For sero-negative primary cases, six to eight salvarsan injections of 0.4 to 0.5 gm. "606" with fifteen calomel (he considered calomel much superior to mercurial cream). For sero-positive primary cases two to three more salvarsan injections, especially when the individual dose in any case was lower than 0.4 gm. For early secondary cases two courses of six salvarsan injections each, with an interval of thirty days between the courses ; in the second course there was usually an interval of three to four weeks after the fourth injection ; two to four injections would be given after this break. The total number of calomel injections appears to have been fifteen to twenty. His paper shows that, while we were increasing our dosage comparatively slowly, his jumped in three years to double or treble ours. Even so, Gennerich's total dosage in terms of arsenic was much less than is being given to-day with results which are by no means so good. I believe that the superiority of his results was attributable to his use of the more efficient salvarsan, in fairly large individual doses and simultaneously with a heavy metal in a form that was likely to be absorbed evenly and at reasonable speed.

In the 1,052 cases which we treated with salvarsan at Rochester Row before the war there was no death or jaundice, and the only instance of a dermatosis was 1 case of transient erythema.

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With regard to neuro-recurrences, only 2 of cranial nerve disturbance occurred. In 1 it was clear that the facial paralysis was an ordinary Bell's palsy, the blood and cerebrospinal fluid being quite negative. In the other the patient had received previously two injections of neosalvarsan followed by 0.3 gm. "606" without any mercury and had developed facial paralysis two months later. We saw 2 other cases of neuro-recurrence that had been treated in other hospitals, each with a single dose of salvarsan, and in one of our papers⁸ we reported that Captain Frost had had 6 in the first 100 cases he had treated with salvarsan. Five of these had had one dose and 1 had had two doses without any other treatment. In 1911 the incidence of neuro-relapse was exciting a great amount of discussion, and Benario²⁰ was prominent in defending "606" against the charge that the increase in cranial nerve disturbances was due to a neurotropic effect of the remedy. In a paper published in 1911 he gave particulars of 118 cases of post-salvarsan cranial nerve disturbance. Besides showing that they were syphilitic, he attributed them to an insufficient treatment, and it is significant that he urged very strongly the use of mercury and iodides in conjunction with salvarsan, as first recommended by Neisser and then by Gennerich, Kromayer and others.

My own experience of neuro-relapse in the form of cranial nerve disturbance and my study of the literature at that time left on my mind the strong impression: (1) That this form of syphilis had increased since the publication of "606" and (2) that it had occurred chiefly if not exclusively in cases treated only with the arseno-benzene compounds. In Gennerich's 1,200 or more cases treated before the war there appear to have been only 2 neuro-relapses with clinical signs. During the war no case treated in either of the two military hospitals I commanded developed a neuro-recurrence, and I cannot remember any such case being shown to me in any of the military hospitals whose treatment of V.D. I had to supervise. I believe that our freedom from this kind of trouble arose from the fact that we gave mercury in conjunction with salvarsan from a very early date in the salvarsan era and that, moreover, we made a practice of starting to give it early in the course of treatment. Since the war, in various papers, I²¹ have contrasted my

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experience in this respect before, during and after the war with that of others who have been less fortunate, and have attributed the difference to the fact that, in early cases, these others have delayed the giving of heavy metal for a number of weeks. I should like to take this opportunity of saying that in early cases treated under my supervision after the war at the St. Thomas's Hospital, the evidence of their practical immunity from clinically manifest neuro-recurrence has now been supported by examinations of a fairly large number of specimens of cerebrospinal fluid taken by medical officers of that Treatment Centre during the time I was its Director. The number of specimens from primary and secondary cases that had received varying amounts of treatment was 270, of which 145 were taken less than twelve months after cessation of treatment and 125 from one to five or more years later. Of the 270 fluids, only one gave a positive Wassermann (with a volume of neat fluid, globulin +, and cells 9 per cm.). One gave a doubtful with two neat volumes (globulin, a trace, and cells 3 per cm.); the remainder gave completely negative reactions, even with two volumes of neat fluid. Of the 268 fluids with completely negative Wassermann reactions the number with six to eight cells per cm. was thirteen; none had more than eight cells. Of the thirteen fluids with six to eight cells, eleven were taken less than twelve months after the last injection, as was also the fluid with a positive Wassermann. This was from a late secondary case which, after an initial course of neoarsphenamine and bismuth, had received a further course of practically only sulpharsphenamine (only 0.4 gm. Bi), and had relapsed five months later with positive serum. He had then again received only sulpharsphenamine for four months before the lumbar puncture. Of the other cases in which the fluid had over five cells per cm., 3 had received less than thirteen arsphenamine and thirteen Bi injections; 3 had received less than twelve arsenical but from ten to forty-six injections of Bi. The remainder had received twelve to twenty-seven arsenical and nineteen to forty-three injections of Bi.

I am glad to see that, in my views on the importance of using heavy metal in conjunction with an arseno-benzene compound in at any rate the early weeks of

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treatment of early syphilis, I am now supported by J. E. Moore,²² whose experience in respect of neuro-recurrences contrasted with my own, and had more or less crystallised my views on this matter. Although Moore, for whose work in this field I have great admiration, remains a convinced adherent to the so-called "continuous" method of treatment, in which courses of arsphenamine alternate with courses of heavy metal, he makes the following concession: "However, it does seem definite that the administration of a small amount of heavy metal early in the course of treatment serves as some protection against the appearance of this particular form of relapse. For this reason I believe that combined treatment with arsphenamine and a heavy metal should be employed during the first few weeks of the management of a patient with early syphilis, and that a short period of combined use does not materially enhance the risk of toxic effects." I am not troubled by his ending up the paragraph by saying: "Following the first course of treatment, however, the two types of drugs should be used in alternation and not together," because, apart from this question of neuro-relapse, with all respect to the work of the American Co-operative Clinical Group, which I admire immensely, their comparisons of the results of continuous treatment practised in U.S.A. with the results of the so-called intermittent treatment which their patients had received do not settle the question of the respective merits of the best form of continuous and the best forms of intermittent treatment. If the so-called "intermittent" treatment employs injections of heavy metal in an insoluble form and, as recommended by the League of Nations Experts Committee, allows intervals between courses of only three to five weeks, it is in effect continuous treatment, because of the continued absorption of heavy metal from the sites of injection during the intervals.

During the war, as opportunity occurred, I increased the course of treatment given to military patients, and then we began to see jaundice and dermatitis. So much has been written on the subject of toxic effects that I do not think any useful object would be served by my discussing them here at any length. It seems now to be clear that, other things being equal, the more intensive the treatment the greater the incidence of jaundice and

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dermatitis, but intensity of treatment and size of dosage are not the only factors, as is shown by the comparative immunity from these troubles of the Danish cases dealt with in the League of Nations Enquiry, in spite of the fact that their individual dosage was higher than ours.

I will not occupy any time discussing treatment with the heavy metals except to say that what I learnt of the effects of injections of mercurial cream and salicylate of mercury would incline me now, if I wanted to include mercurial injections in a patient's treatment, to use calomel, as recommended by Gennerich. With regard to bismuth compounds, all one's experience tends to show that the violent but evanescent effect of the arseno-benzene preparations ought to be supplemented by a more persistent, if milder, effect of heavy metals, and this suggests the use of insoluble rather than soluble compounds.

To sum up these experiences in the treatment of early syphilis, when I contrast the effects of our best pre-war course of salvarsan and mercury and especially Gennerich's results with those of the present-day courses of "914" with bismuth, it does occur to me that we might consider if it would not be better to use fewer but comparatively large doses of an arsphenamine preparation, perhaps separating each pair by two weeks or so of treatment by a heavy metal. Also the contrast between therapeutic effects of "606" and of "914" given intravenously makes one wish it was practicable to give "606" in our clinics. As we cannot, because of side effects, and as, after all, "914" given subcutaneously seems to give results that are as good, research to find a tolerable method of giving it by this route seems likely to be well worth while. I say neoarsphenamine for the subcutaneous route and not sulpharsphenamine advisedly, because I do not believe the therapeutic effect of the sulpharsphenamine preparation to be nearly so good. On the question of alternating arseno-benzene courses with courses of heavy metal *versus* the concurrent use of both types in early cases, I remain a convinced adherent to the concurrent plan, and emphatically so in the first course of treatment.

So far I have spoken of experiences in the treatment of early cases and have occupied so much time in it that there is too little left to deal adequately with late cases,

but here I would mention a thing which experience has taught me to be most important. It is to examine the cerebrospinal fluid of every case of syphilis with an infection of more than four years' duration. Whatever one may think of the importance of examining the fluid of early cases that have been well and regularly treated, there is no question of its necessity in the later cases if one does not want the mortification of occasionally seeing a late case of syphilis that one has treated regularly for many months with the ordinary trivalent arsenical preparations develop G.P.I.

It is interesting that in the beginning of the salvarsan era the pentavalent arsenicals were taboo because of a neurotropic effect, and that now (Fig. 6) in the form of

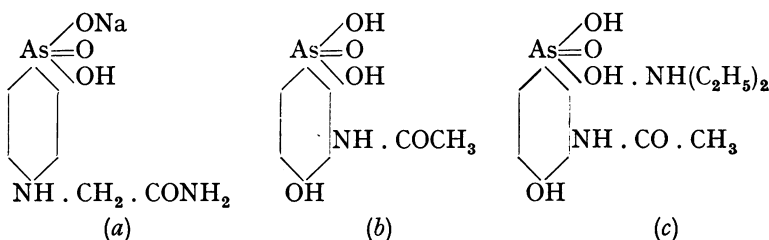


FIG. 6.—(a) Sodium N-phenylglycineamide-p-arsenate, or **Tryparsamide**. (b) 3-Acetylamino-4-hydroxyphenylarsonic acid (No. 594 of Ehrlich's series, No. 190 of Fourneau's) or Acetarsonone. Sold as **Stovarsol Orarsan, Spirocid, or Kharophen**. (c) Diethylamine salt of acetarsonone, or **acetylarsan**.

tryparsamide, acetylarsan, stovarsol (spirocid, kharophen or orarsan) they are the arsenicals we prefer in late neuro-syphilis.

When the examination of the spinal fluid becomes routine in these late cases and the treatment is guided thereby, there will be some reduction in the incidence of late neuro-syphilis.

Lastly, I would heartily endorse the remarks made here some months ago by Dr. Osmond²³ on the merits of the Sigma test as a gauge of the effects of treatment in late cases. By the Sigma method the strength of the reaction is automatically expressed by a numeral. Consequently, instead of the serum at the end of course after course being reported as strongly positive, with no indication of any weakening, as occurs with such tests as the Wassermann and the Kahn, the Sigma shows usually a steady lowering of the number which indicates the

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strength of the reaction in a way that encourages both the patient and his physician.

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